PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ON/4-33584A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2005/001849	International filing date *(day/month/year)* 22.02.2005	Priority date *(day/month/year)* 23.02.2004
International Patent Classification (IPC) or national classification and IPC C12Q1/68, G01N33/574		
Applicant NOVARTIS AG et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.12.2005	19.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Mueller, F Telephone No. +49 89 2399-7722

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/001849

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-16 as originally filed

   Sequence listings part of the description, Pages

   1-2 as originally filed

   Claims, Numbers

   1-14 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item I

Basis of the report

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: HUANG S ET AL:DRUG RESISTANCE UPDATES, vol. 4, no. 6, December 2001 (2001-12), pages 378-391
D2: US-B1-6 521 407
D3: HOSOI H ET AL: CANCER RESEARCH, vol. 59, no. 4, 15 February 1999 (1999-02-15), pages 886-894
D4: HUANG S. ET AL.,: CANCER RESEARCH, vol. 61, 15 April 2001 (2001-04-15), pages 3373-3381
D5: HOSOI H. ET AL.,: MOLECULAR PHARMACOLOGY, vol. 54, 1998, pages 815-824,
D6: WO 02/066019 A
D7: TIAN H ET AL: CANCER RESEARCH, US, vol. 60, no. 3, 1 February 2000 (2000-02-01), pages 679-684,

D6 describes the use of a combination of rapamycin and e.g cis-platin or gemcitabine, see p. 12, for the treatment of A549 cancer cells. A549 cells are also used in the present application as support for the claimed method, see e.g. example 1. A549 are p53 wild-type. The use of a p53 wild-type cancer cell line which is sensitive for a treatment of a combination comprising a mTOR inhibitor and a cytotoxic agent is considered to be inherently disclosed in D6. Furthermore the combination of D6 results in the same technical effect, namely a sensitivity of this cancer type for this specific combination.
No inventive step for the subject-matter of claim 1 can therefore be acknowledged (Art. 33(3) PCT). The same holds true for claims 2-10.
In addition D2 describes a method for evaluating the sensitivity of cancer cells for a certain

method of treatment (e.g. platining agents) by evaluating the expression of specific factors (e.g. p53 nd p21), see claims.
D1 describes the use of rapamycin for the treatment of cancer and discusses that the p53 status is relevant for rapamycin sensitivity, see e.g. abstract, p.384, 2. col.,
D3 describes the use of rapamycin for the treatment of cancer cells, e.g. NB-1643 (p53 wild-type) after radiation, see p.889, 1. col. and furthermore discusses the relation (expression, induction) of p53 and p21, see e.g. Fig. 3. D3 also describes that the rapamycin-induced apoptosis is p53 independent, see e.g. p.892, 2. col.
D4 describes the effect of p53 and p21 expression in cancer cells for their sensitivity to a rapamycin treatment, see .e.g. p.3373, 2.col., last par.ff and p.3375, 2.col., 2. par. and p.3380, 1. col., 2. par.
D5 describes the use of rapamycin for the treatment of NB-1643 (p53 wild-type) cells, see e.g. Table 1, p.817.

Without the indication of a special technical effect of the claimed subject-matter with respect to D1-D5, the disclosures of D1-D5 are considered to be relevant with respect to inventive step. An inventive step of claims 1-14 can therefore not be acknowledged (Article 33(3) PCT).

Re Item VIII
Certain observations on the international application

- The subject-matter of claim 1 is not clear (Article 6 PCT). The term "p53 status" is not defined (TP53 is considered to be the wild-type form) and therefore renders the scope of claim 1 unclear.

- The subject-matter of claim 3 is not clear (Article 6 PCT). The relation of sensitivity and p53 status is not defined by functional and/or structural features and therefore renders the scope of claim 3 unclear.
  The same holds true for claim 7.

- The subject-matter of claim 11 is not clear (Article 6 PCT). The relation of p21 and sensitivity to a treatment is not defined by structural and/or functional features and

therefore renders the scope of the claim unclear.
The same holds true for claim 13.